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Management of Atrial Fibrillation in Patients with Kidney Disease

Yee C Lau, Gregory Y H Lip

University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom.

Abstract

The increasing burden of Chronic Kidney Disease (CKD) is highly relevant to cardiologists, as cardiovascular mortality is 10-30 times higher amongst people with End-stage Renal Disease (ESRD), comparing with general population. One of the commonest associations is the increased frequency of atrial fibrillation (AF) amongst those experiencing CKD.

Overall, we know that AF is the most common cardiac arrhythmia. AF leads to a substantial risk of mortality and morbidity, from stroke and thromboembolism, heart failure, reduced cognitive function and impaired quality of life. However, most clinical trials in AF (for example, for stroke prevention in AF with anticoagulation therapy) have largely excluded patients with significant renal impairment.

In this review article, we will focus on stroke prevention in AF, and the clinical impact of CKD and its implications for management.

Introduction

Chronic Kidney Disease (CKD) is defined as a reduction in renal function, with a reduction in glomerular filtration rate(GFR) <60ml/min per 1.73m^2 for 3 months or longer, the presence of albuminuria, or both.[1] The classification scheme of CKD stage 1-5 is traditionally based on glomerular filtration rate, with CKD stage 1 being one with preserved renal function (GFR >90ml/min) to CKD stage 5 being one with the worst renal function (GFR <15ml/min).[2] Those with CKD stage 5, with accompanying signs of fluid and electrolyte imbalance, necessitates renal replacement therapy (eg. dialysis) and is classified as End-stage Renal Disease (ESRD).

CKD is increasingly being recognised as an important cause of death and morbidity globally. The prevalence of CKD is estimated to be between 8-16% globally and its upward trajectory has led to the rise in mortality (CKD listed as 27th in list of causes of total number of global death in 1990, to 18th in 2010) as well as increasing loss of disease adjusted life years.[3] An important reason is the improving longevity and expansion in number of elderly people in the world. This trend is further exacerbated by the increasing incidence of diabetes and hypertension (which are the leading causes of CKD) in both developed and maturing economies, the lack of access to effective healthcare resources and low awareness of renal disease amongst the at risk population.[1,4-5] Without an effective prevention and management strategy, CKD is rapidly becoming a global public health issue.

Besides nephrologists, this increasing burden of CKD highly relevant to cardiologists, as cardiovascular mortality is 10-30 times higher amongst people with ESRD, comparing with general population.[3] One of the commonest associations is the increased frequency of atrial fibrillation (AF) amongst those experiencing CKD.

Overall, we know that AF is the most common cardiac arrhythmia. AF leads to a substantial risk of mortality and morbidity, from stroke and thromboembolism, heart failure, reduced cognitive function and impaired quality of life.

Nevertheless, most clinical trials in AF, for example, for stroke prevention in AF with anticoagulation therapy have largely excluded patients with significant renal impairment. In this review article, we will focus on stroke prevention in AF, and the clinical impact of CKD and its implications for management.

The Size Of The Problem

The prevalence of AF rises from 0.7%[6] in general population age <60, to 27%[7] amongst those with ESRD. Despite the presence of significant variability, the relationship AF among patients with CKD have been substantiated and independently verified by several studies.[8-10]

In the larger Chronic Renal Insufficient Cohort (CRIC) study in America, involving almost 3300 patients with CKD, nearly 20% have evidence of AF.[10] The Atherosclerosis Risk in Community (ARIC)

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Disclosures:
Prof Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

Corresponding Author:
Professor Gregory Y H Lip
University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham, B18 7QH, United Kingdom

Study has also shown that patients with GFR of 60 - 89, 30 - 59, and 15 - 29 mL/min/1.73 m^2 have hazard ratios of developing AF (within the 10 year follow-up period) of 1.3, 1.6, and 3.2, respectively, as compared to those with normal GFR. This further reinforces the association between reduced renal function and incidence of AF.[11]

In addition to increase of the risk of ischaemic stroke and thromboembolic event, the diagnosis of AF in pre-existing CKD also heralds early deterioration of renal function and risk of progression to ESRD.[12-13] Henceforth, a bidirectional relationship between AF and CKD may exist. As one begets the other, the presence of both conditions has shown to result in even higher stroke and mortality risk.[14] The 1-year mortality rate for patients with CKD Stage 3-5 with incident AF is as high as 35.6%.[15]

Thromboembolism In AF And CKD: Pathophysiological Insights

The presence of AF confers the presence of a prothrombotic hypercoagulable state through numerous pathophysiological pathways.[16] The propensity of thrombus formation (thrombogenesis) can be described in relation to a triad of abnormalities first described by Virchow 150 years ago, hence this being referred to as 'Virchow's triad for thrombogenesis'.[16]

First, abnormalities of flow, caused by blood stasis within the left atrium and adjoining left atrium appendage. Second, abnormalities within the vessel wall, with structural heart disease macroscopically and – at a more microscopic level - endothelial or endocardial damage/dysfunction including increase expression of von Willebrand factor or tissue factor. The third component of Virchow's triad refers to abnormalities of blood constituents, with abnormal coagulation, platelets and fibrinolysis (Table 1).

In CKD, many other potential contributing factors appear to contribute to this increased thromboembolic risk, for example, the up-regulation of rennin-angiotensin-aldosterone-system (RAAS) and chronic inflammation.[17] The RAAS is demonstrated to be up-regulated in hypertensive state,[18] and together with chronic elevation of inflammatory markers through various stages of CKD,[19-20] would led to the propagation of a prothrombotic state and consequently bring about an increase in the propensity to thrombogenesis. Additionally, the increase in thromboembolic risk may also be caused by chronic vascular calcification and/or dysfunction of calcium-phosphate metabolism in CKD.[21-22]

Given the above-mentioned pathophysiological pathways, the elevated thromboembolic risk will undeniably result in an increased risk of ischaemic stroke and thromboembolism.

Thromboembolism In AF And CKD: Clinical Insights

The close relationship between thromboembolism and CKD amongst AF patients has been reported by several large observational studies.

In the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study, Go et al.[33] found that proteinuria increased risk of thromboembolism by 54%; and progressive worsening of GFR is also associated with increased risk of stroke, so much so that those with GFR <45 mL/min/1.73 m^2 confers a increased risk of 39% as compared to those with normal GFR.

Table 1: Pathophysiologic Mechanisms of Thromboembolism in Chronic Kidney Disease

Study	Study Type	N	Population	Findings
			Blood Stasis in Left Atrium	
Yagishita et al [23] (2010)	Observational	321	Patients with persistent atrial fibrillation	GFR an independent predictor of reduced left atrial appendage emptying velocity and presence of left atrium spontaneous echo contrast
Providência et al [24] (2013)	Observational	372	Patients with nonvalvular atrial fibrillation	eGFR is positively associated with dense spontaneous echocardiographic contrast, and low flow velocities in the left atrial
			Endothelial Dysfunction	
Hrafnkelsdóttir et al [25] (2004)	Comparative	18	Non-diabetic, non-smoking CKD pt and age-matched control	Maximal release of active tPA and capacity for active tPA release markedly impaired in CKD pts vs controls
Heintz et al [26] (1994)	Comparative	40	CKD and healthy controls	CKD pts have higher endogenous levels of ET-1, plasma cAMP, and enhanced ET-1 stimulated ADP-induced platelet aggregation than healthy control
Carrero et al [27] (2012)	Observational	630	NDD CKD vs ESRD	Prolactin levels increased along with reduced kidney function, related to FMD, PWD and increased risk of cardiovascular events and mortality.
Recio-Mayoral et al [28] (2011)	Comparative	141	76 CKD vs 65 age and gender matched control	CKD patients had increased CRP levels, reduced FMD and increased IMT values compared to controls
			Platelet activation and coagulation abnormalities	
Shlipak et al 19 (2003)	Cross-sectional	5888	Population-based cohort of age >65 y	CRP, fibrinogen, IL-6, Factor VII, Factor VIII, plasmin-antiplasmin complex, and D-Dimer levels significantly higher in CKD
Keller et al[20] (2008)	Cross-sectional	6814	Population-based cohort 45-84	CRP, IL-6, TNF, TNF-αR1, intercellular adhesion molecule-1, fibrinogen, and Factor VIII levels are significantly higher in CKD
Landray et al [29] (2004)	Comparative	522	334 CKD pts, 92 CAD pts, 96 healthy control with no prior CV or renal disease	CKD is associated with higher fibrinogen, plasma vWF, soluble P-selectin, but not CRP
Tanaka et al [30] (2009)	Observational	190	Pts not receiving oral anticoagulant stratified to CCr	Decreased GFR predicts for elevation of TAT and D-Dimer in pts with AF
Mercier et al [31] (2001)	Cross-sectional	150	50 ESRD pts, 50 NDD CKD and 50 healthy controls	Reduced renal function associated with enhance tissue factor coagulation to platelet, monocyte and endothelial injury.
Adams et al [32] (2008)	Comparative	102	66 CKD stage 4&5 vs 36 healthy controls	Up-regulation of the tissue factor pathway, increased prothrombin fragment 1+2 and reduction in antithrombin III in CKD compared to healthy controls

Abbreviations: ADP, adenosine diphosphate; AF, atrial fibrillation; CAD, coronary artery disease; cAMP, cyclic adenosine monophosphate; CCr, Creatinine clearance; CKD, chronic kidney disease; CV, cardiovascular; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESRD, End-stage renal disease; ET-1, Endothelin 1; FMD, flow-mediated dilation; GFR, glomerular filtration rate; HD, haemodialysis; IL-6, interleukin-6; intima-media thickness, IMT; MDRD, Modification of Diet in Renal Disease; NDD, non-dialysis dependent; pt, patient; PWV, pulse wave velocity; TAT, thrombin-antithrombin complex; TNF-αR1, tumour necrosis factor-α soluble receptor 1; tPA, tissue plasminogen activator; vWF, von Willebrand factor.

In the Danish nationwide cohort study, Olesen et al.[34] found that those AF patients with CKD had significantly higher rate of stroke, thromboembolism, bleeding and death, as compared with those without renal disease. The risks were substantially higher if renal replacement therapy was needed (Table 2).

Amongst those with CKD (GFR <60ml/min per 1.73m^2), the sequential deterioration of renal function over time has been shown to be associated with an increased risk of clinical adverse events.[13] Indeed, an absolute reduction in eGFR ≥25 mL/min/1.73 m^2 or a relative reduction of eGFR ≥25% effectively more than doubles the risk of ischaemic stroke when compared to those with relatively "stable" renal function over 6 months period.

Recent evidence also revealed that GFR is not only can be an independent, reliable predictor of stroke mortality,[35] but CKD also results in a more adverse clinical outcome after stroke, such as increased neurological deterioration or worsen functional outcomes.[36-37]

Bleeding Risk In CKD

Even though CKD does increase the risk of thromboembolism and ischaemic stroke, the presence of this condition is also associated with an important increased risk of intra-cranial or gastrointestinal haemorrhage.

In both the Rotterdam Study,[39] as well as the Japanese CIRCS Study,[40] the presence of reduced renal function (GFR <60 mL/min/1.73 m^2) resulted in an increased risk of haemorrhagic stroke in males, with reported hazard ratios of 4.10 and 4.18, respectively. The hazard ratio of haemorrhagic stroke in females is even higher, in excess of 7.00.

Current imaging modalities have also revealed that patients with CKD possess an increased in presence and numbers of MRI-defined cerebral microbleeds (CMB), which are actually harbinger of potential intra-cranial haemorrhage.[41] Even for those who have experienced an acute ischaemic stroke, lower GFR levels (<30 mL/min/1.73cm^2) are found to have an association with haemorrhagic transformation, with an odds ratio of 2.90 (95% CI 1.26-6.68).[42]

Table 2: Stroke Risk in patients with AF with CKD

Stroke Risk in AF with CKD			
Study	**Study Type**	**N**	**Findings**
Go et al 33(2009)	Retrospective	10908 AF with CKD	Comparing with GFR ≥ 60 mL/min/1.73 m^2: eGFR 45-59mL/min, RR 1.16 (95% CI, 0.95 to 1.40) eGFR < 45mL/min, RR 1.39 (95% CI, 1.13 to 1.71 (P = 0.0082 for trend).
Friberg et al 38 (2012)	Retrospective	182678 AF pts	CKD Stage 1 and below: Multivariate HR 1.11(95% CI 0.99-1.25)
Olesen et al 34 (2012)	Retrospective	132372 AF pts (out of which 3587 NDD CKD, 901 ESRD)	Comparing with GFR ≥ 90 mL/min/1.73 m^2: NDD CKD, HR 1.49 (95% CI 1.38-1.59) ESRD, HR 1.83 (95% CI, 1.57 to 2.14)
Guo et al 13 (2013)	Prospective	617 AF pts	Risk of stroke or death: HR 2.90 (95% CI 1.88-4.48) Risk of stroke in 6 months: Absolute decrease eGFR ≥ 25 mL/min/1.73 m^2: HR 2.77 (95% CI 1.26-6.09) Relative decrease eGFR ≥ 25%: HR 2.57 (95% CI 1.14 – 5.80)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; NDD, non-dialysis dependent; pts, patients; RR, relative risk

Table 3: The CHA_2DS_2-VASc score

Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes Mellitus	1
History of Stroke/TIA/thromboembolism	2
Vascular disease (previous myocardial infarction, peripheral vascular disease or aortic plaque)	1
Age (64-74 years)	1
Sex category (female)	1

Maximum score 9

For gastrointestinal bleeding, the recurrence, frequency and severity of such bleeds is linked to the reduction of renal function.[43 - 44]Indeed, CKD and ESRD also predict higher risk of mortality as a sequalae of gastrointestinal bleed, with corresponding odds ratios of 1.47 (95% CI 1.21-1.78) and 3.02 (95% CI 2.23-4.1), respectively.[44]

The causes of increased risk of haemorrhage in CKD are multifold. It could be the concurrent use of anti-platelets or non-steroidal anti-inflammatory drugs, as a result of uremic toxins in ESRD,[45] or increased vascular ectasia and angiodysplasia.[46-47] Other pathophysiological causes of increased bleeding risk which have been proposed include platelet dysfunction, impaired platelet aggregation and adhesion, abnormal intraplatelet calcium mobilisation, impaired release of platelet alpha-granule protein, impaired platelet glycoprotein IIb IIIa receptor activation and its binding to glycoprotein and altered von Willebrand factor.[48-49] In addition, patients at the terminal end of CKD (ESRD) will be subjected to an increased frequency of invasive diagnostic and treatment strategy, such as haemodialysis or central venous access, which consequently increases their propensity to bleed.

In summary, worsening renal function, from CKD to ESRD, has a graded relationship with an increase bleeding tendency. Thus CKD per se been shown to precipitate an increase in intra-cranial bleed, gastrointestinal haemorrhage and all cause mortality.

Risk Stratification for Stroke in AF with CKD

Despite the increased risk of ischaemic stroke and thromboembolism due to AF, this risk is not homogeneous and depends on the presence of several common stroke risk factors. Stroke risk can be evaluated by clustering of various risk, factors leading to several stroke risk stratification schemes being derived.

A commonly used stroke scoring system has been the $CHADS_2$ score, confers 1 point to each risk factor, and for each point corresponds to an approximate factor of 1.5 fold increase in stroke rate per 100 patient-years. However, the $CHADS_2$ score has various limitations since been superseded by CHA_2DS_2-VASc score, which is

Table 4 : The HAS-BLED Score

Hypertension	1
Abnormal renal and liver function (one point each)	1
Stroke	2
Bleeding history or propensity	1
Labile INR	2
Elderly (age > 65 or frail condition)	1
Drugs or alcohol concomitant use (one point each)	1

maximum score 9

Table 5: VKA use and stroke rates in ESRD

VKA use in AF with ESRD			
Study	Study Type	Number (% with AF)	Findings
Wiesholzer et al 58 (2001)	Retrospective observational	430 (14.3%)	Stroke rate per 100 patient year: AF with VKA: 4.46, AF without VKA: 1.0
Abbott et al 59 (2003)	Retrospective observational	3374 (1.25%)	3-year survival rate: AF with VKA: 70% AF without VKA: 55%
Chan et al 60 (2009)	Retrospective observational	48825 (3.42%)	90-day HR – AF with VKA a: 2.75 (95% CI 1.49 – 5.08)
Winkelmayer et al 6162 (2011)	Retrospective observational	[2313 ESRD patients with new AF]	HR for ischaemic stroke: VKA user 0.92 (95% CI 0.61 – 1.37)
Olesen et al 34 (2012)	Subgroup analysis	[901 patients with AF requiring dialysis]	HR comparing with no antithrombotic, dialysis dependent pts:
Sood et al 6263 (2013)	Observational	Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/ abuse	1 or 2

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DOPPS, Dialysis Outcomes and Practice Pattern Study; HR, hazard ratio; VKA, Vitamin K antagonist
a AF with VKA covariate adjusted model: adjusted for CHADS2 score, gender, race, Charlson comorbidity index, entry date, body mass index, facility standardised mortality ratio, cardiovascular drugs, dialysis adequacy, baseline laboratory values, heparin dosage and heparin regimes.
b VKA user includes patients with atrial fibrillation, thromboembolic disease or central vascular catheter.

more inclusive of common risk factors and given various limitations of the $CHADS_2$ score in particularly in defining those at 'low risk'.

The CHA_2DS_2-VASc (Table 3) is recommended by the European Society of Cardiology AF guidelines,[50] and on the other hand, performs better than the $CHADS_2$ score in predicting stroke and thromboembolism especially in identifying those truly 'low risk' patients with AF who will not benefit from antithrombotic therapy.[38,51] The European guideline recommended that anticoagulation is not needed if the CHA_2DS_2-VASc score is 0 in males or 1 in females, as such patients are low risk. Subsequent to the identification of low risk patients, effective stroke prevention can be offered to those with ≥1 stroke risk factors, and thus, oral anticoagulation should be considered with those with a CHA_2DS_2-VASc score of 1 and above.

However, CKD or moderate-severe renal impairment is not currently been included in the $CHADS_2$ or CHA_2DS_2-VASc scores, despite been recognised as a contributor to thromboembolic risk. This is due to the limited data (at least when the scores were being derived and/or validated) and the exclusion of those with significant renal impairment from the major clinical trials. Nonetheless, much more attention has been directed to CKD as a contributor to stroke risk given its co-existence with AF in many patients.

There are ongoing attempts to incorporate renal impairment into stroke risk stratification schemes. For example, Piccini et al.[52] proposed a new model to include creatinine clearance into stroke prediction, with the R_2CHADS_2 score, where the addition of "R" signifies impaired renal function, and adds 2 points to the $CHADS_2$ score. Piccini et al showed that impaired renal function is a strong and independent predictor of stroke and systemic embolism, the R_2CHADS_2 score improved the $CHADS_2$ and CHA_2DS_2-VASc c-indexes (a statistical measure of how good a score predicts events, with 1.0 offering perfect prediction whilst a c-index of 0.5 is 50:50 chance), but only very marginally. Nonetheless, the R_2CHADS_2 score was derived from an anticoagulated clinical trial population, and the independent impact of a stroke risk factor should be evaluated in a non-anticoagulated cohort. Also, the ROCKET-AF trial[68] excluded those with severe CKD (creatinine clearance <30mls/min) and did not recruit a wide spectrum of AF stroke risk, given that the trial inclusion criteria mandated a $CHADS_2$ score of ≥2 and the proportion with a score=2 was capped at 10%.

Similar relationship between renal impaired and stroke risk was suggested in the ATRIA stroke risk score,[53] and as well as the R-CHA_2DS_2-VASc score (albeit in patients with prior myocardial infarction).[73] The studies in selected cohorts confirm some additive value of adding CKD or renal impairment to the $CHADS_2$ and/or CHA_2DS_2-VASc scores, but again, only improved the c-indexes very marginally.

Additional studies in 'real world' AF cohorts that included non-anticoagulated AF patients with a broad range of stroke risk and renal function do confirm an increased even rate with CKD or moderate-severe renal impairment in AF patients, but this did not independently improve the predictive value of $CHADS_2$ and CHA_2DS_2-VASc score.[54-55] After all, CKD is commonly associated with age, heart failure, diabetes, vascular disease etc – which are all components of the CHA_2DS_2-VASc score.

Risk Stratification for Bleeding in AF: The HAS-BLED Score

Stroke and bleeding risk in AF are closely related to each other. In the presence of AF, the European guidelines recommend the use of the HAS-BLED score for assessing bleeding risk (Table 4). A high HAS-BLED score is used to 'flag up' the patients potentially at risk of bleeding for careful review and follow-up, and to make clinicians think about the potentially correctable risk factors such as uncontrolled hypertension (the H in HAS-BLED) or labile INRs in those patients on warfarin. A high HAS-BLED score per se should not be a reason to withhold oral anticoagulation therapy.

In HAS-BLED, renal failure was defined in validation cohorts as those requiring long-term dialysis, renal transplant and serum creatinine over 2.26mg/dL, given the risk of bleeding diathesis. Nonetheless, a more simple and practical approach is to consider 'abnormal renal function' in HAS-BLED as those with severe renal impairment or significant proteinuria.

Table 6: VKA use and stroke/thromboembolic event rate in non-dialysis dependent CKD

VKA and event rate in non-dialysis dependent CKD			
Study	Study Type	Number	Findings
Lai et al 63 (2009)	Observational	307	Stroke event rate (% per year): Dose-adjusted warfarin (INR target 2-3): 3.48 No VKA: 13.57
Hart et al 64 (2011)	Post-hoc analysis	516	Stroke/embolic event rate (% per year): Dose-adjusted warfarin: 1.45 Dose-adjusted warfarin plus aspirin: 7.05
Olesen et al 34 (2012)	Subgroup analysis	3587	HR of stroke comparing with no antithrombotic NDD CKD: Warfarin only: 0.84 (95% CI 0.69 – 1.01) Warfarin plus aspirin: 0.76 (0.56 – 1.03) Aspirin only: 1.25 (1.07 – 1.47)

Abbreviations: CKD, chronic kidney disease; INR, international normalised ratio; NDD, non-dialysis dependent; VKA, vitamin K antagonist

Table 7: Randomised Controlled Trials for Novel (or non-Warfarin) Oral Anticoagulants in AF

Study	Connolly et al 65 (2009)	Connolly et al 66 (2011) AVERROES	Granger et al 67 (2011) ARISTOTLE	Patel et al 68 (2011) ROCKET	Giugliano et al 69 (2013) ENGAGE
Number	18113	5999	18201	14264	21108
Dosage	Dabigatran 150 mg twice daily Dabigatran 110mg twice daily Dose-adjusted Warfarin	Apixaban 5mg twice daily Aspirin 81-324mg daily	Apixaban 5mg twice daily Apixaban 2.5mg twice daily (eGFR <50mL/min) Dose-adjusted Warfarin	Rivaroxaban 20mg once daily Rivaroxaban 15mg once daily(eGFR 30-49mL/min) Dose-adjusted Warfarin	Edoxaban 60mg once daily Edoxaban 30mg once daily Dose-adjusted Warfarin
F/U (months)	24	13.2	21.6	23.5	Median F/U 2.8 years
CKD stages studied	eGFR 30-50mL/min eGFR 50-79mL/min	eGFR 30-60mL/min	eGFR 25-30mL/min eGFR 31-51mL/min eGFR 51-80mL/min	eGFR 30-49mL/min eGFR ≥50-mL/min	eGFR 30 - ≤50mL/min
Pharmacokinetics	80% renally excreted	25% renally excreted	25% renally excreted	33% renally excreted	35% renally excreted
Key Results (Event rate %/year)	Superior to warfarin in reducing ischaemic stroke and thromboembolism (1.11 vs 1.53 vs 1.69) Non-inferior in bleeding events (3.11 vs 2.71 vs 3.36)	Superior to warfarin in reducing ischaemic stroke and thromboembolism (1.6 vs 3.7) Non-inferior in bleeding events (1.4 vs 1.2)	Superior to warfarin in reducing ischaemic stroke and thromboembolism (1.27 vs 1.6) Lower incidence of bleeding events (2.13 vs 3.09)	Non-inferior to warfarin in reducing ischaemic stroke and thromboembolism (2.2 vs 2.4) Non-inferior in bleeding events (14.9 vs 14.5)	Non-inferior to warfarin in both doses in reducing ischaemic stroke and thromboembolism (1.49 vs 1.91 vs 1.69) Lower incidence of bleeding events (2.75 vs 1.61 vs 3.43)
Outcomes for CKD pts	No difference in primary outcome	Lower stroke risk with no increase in bleeding risk	Non-inferior in stroke risk, but reduced bleeding risk for eGFR >30mL/min	No difference in primary outcome	Lower bleeding risk at reduced dose

Given that the risk of ischaemic stroke and thromboembolism is closely intertwined with bleeding risk amongst CKD patients, [56] those with CKD might potentially receive greater absolute risk reduction of ischaemic stroke or systemic thromboembolism from anticoagulation, which outweighs the smaller absolute increase in serious bleeding risk.[38]

Oral Anticoagulation in CKD: Using Vitamin K Antagonists (VKA)

Oral anticoagulants are generally indicated in the general population with AF, for stroke prevention. However, is it feasible for the same to be recommended for those with CKD? The current recommendations and guidelines are drawn from cohort studies and extrapolations of results from clinical trials in the general AF population, as little evidence exists for those with severe renal impairment given that such patients were exclude from randomised trials.

Unsurprisingly, the prescription of anticoagulants (essentially Vitamin K antagonists eg. warfarin) amongst those with significant renal impairment varies from as low as 2% in Germany to as high as 37% in Canada.[57] This heterogeneity in clinical practice reflects the uncertainty about the risks and benefits of anticoagulation use within this patient group.

Amongst CKD patients undergoing dialysis, there remain significant conflicting findings from various observational studies regarding the safety associated with use of VKA (Table 5). Besides Abbott et al[59] showing a mortality benefit and Olesen et al[34] demonstrating a reduction event rate for stroke or thromboembolism, other studies involving ESRD and VKA thromboprophylaxis have even suggested that VKA can potentially cause harm in CKD patients with ESRD.[60-62] patients were exclude from randomised trials.

Large observational studies[60,62] have demonstrated that dialysis patients who are on Warfarin experience more than two-fold increase in the risk of ischaemic stroke as compared to non-VKA users. As shown by Winkelmayer et al[61] this increase in stroke risk may be secondary to haemorrhagic stroke rather than thromboembolic cerebral events.

The other possible explanations for this increase in stroke risk amongst VKA users may be due to the lack of close monitoring[60] of the International Normalised Ratio (INR) amongst at risk group during warfarin initiation, thus potentially resulting in reduced time in therapeutic range. Without further randomised control trials, the propensity for harm due to VKAs is yet to be fully understood.

Conversely, amongst non-dialysis dependent CKD patients, there appears to be more robust data favouring the use of dose-adjusted VKA in AF (Table 6). In all 3 observational studies, dose-adjusted warfarin provided better ischaemic stroke and systemic embolic protection, than non-users.[34,63-64] However, the use of warfarin amongst the Danish study cohort[34] appears to significantly increase the tendency of bleeding by 36%, the event rate was further increased with concurrent use of both aspirin and warfarin (63%).

Novel Oral Anticoagulants

Over the past few years, the landscape of stroke prevention in AF had dramatically changed with the introduction of novel (or non-warfarin) oral anticoagulant agents (NOACs), specifically the direct thrombin inhibitor (dabigatran) and Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban).

All four agents have been shown non-inferiority or even superiority in stroke prevention, and non-inferiority (or in some cases, superiority) in bleeding profile as compared to warfarin.[65-69] Similar data exists even for those with varying degree of reduced renal function (eGFR 30-50mL/min) (Table 7). For example, a subgroup analysis of the ARISTOTLE trial for the use of apixaban in patients with significant CKD (eGFR 30 - ≤50mL/min) had demonstrated a marked reduced bleeding risk, as compared to warfarin. Additional benefits include medication delivery in fixed doses, not requiring monitoring, and have a lower propensity for interaction with food or other medications [70-71]

The most important caveat in all these trials is such that patients with ESRD or significant CKD (with creatinine clearance ≤25-30mL/min) were all excluded, thus making the extrapolation of the results to those with severe renal dysfunction hazardous, particularly since all agents have a degree of renal excretion. The latter varies from approximately 25% renal excretion with apixaban, to 33% with rivaroxaban, to 50% with edoxaban and 80% with dabigatran.

Based on no clinical trial outcome data but pharmacological modelling in patients with a creatinine clearance of 15-29mls/min, dabigatran 75mg bid is approved for AF patients in USA for those with a creatinine clearance 15-30mls/min. Similarly rivaroxaban 15mg od and apixaban 2.5mg bid is approved for use in moderate renal impairment (15-29 mls/min), with caution advised with regard to watching for bleeding risk.

Another oral Factor Xa inhibitor, betrixaban is currently being studied in a Phase 3 randomsied trial in acute medically ill patients (but not AF per se) but this drug is only minimally renal excreted.[72]

Conclusions:

The management of patients with both CKD and AF is often difficult, as not only do these 2 conditions have a close relationship, with an increase in thrombotic and haemorrhagic risks with sequential reduction in renal function. The risk of both ischaemic and bleeding events are particularly high amongst dialysis dependent patients with ESRD. However, there is increasing evidence that anticoagulation use among non-dialysis dependent CKD patients with AF can reduce morbidity and mortality from stroke and systemic thromboemobolism.

The key would be for careful patient selection through the utilisation of risk stratification scores (CHA_2DS_2-VASc and HAS-BLED scores). Even those with ESRD may potentially benefit from anticoagulation, provided that substantial steps are taken to reduce bleeding risk (such as rigorous INR checks, aiming for a high Time in Therapeutic Range, >70%[74-75]).

With the rapidly aging global demographics, the burden of disease will only increase, but there still remains relatively limited evidence regarding thromboprophylaxis in those patients with the most severe renal dysfunction. Despite the great potential for NOACs,[76-77] further outcome data are needed in those with severe renal impairment and such information may eventually become evident from ongoing registries and post-marketing studies.[78-79] Time will tell.

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